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Biological Warfare: History and Current Developments

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Biological warfare (BW) is the deliberate promulgation of infectious agents to make war. Defence against BW attacks will call on the utmost of our moral as well as technological ingenuity.

Introduction

The technical aspects of biological weapons and biological warfare (BW) are the province of specialties like infectious diseases, public health, forensics and military strategy. Ample information resources provided by those specialists can be found in print monographs, and on the World Wide Web. Some may argue that too much information is readily available, since there is no limitation of access on the part of would-be perpetrators. That is inevitable, since knowledge needed for the practice of BW is virtually congruent with that needed for our struggle with natural infection. It is also vital for our understanding of the ecological relationship of the human organism, and its collective population, with the biosphere. There can be no escaping microbes, which have varied potential for supporting health or disease: indeed each human genome sustains a body space which harbours hundreds or thousands of ancillary species, namely our microbiome.

BW is the deliberate promulgation of infectious agents to make war. The attacks of and since 11 September 2001 have dragged the most sceptical among us to the insight that these weapons are no longer the monopoly of superpowers. They may be invoked by a range of threators – down to single individuals. Even the isolated threator, we now perceive, may bring about a level of violence, fear and disruption that we had previously arrogated only to states. Thus concern about BW has permeated every stratum. Lay folk will look to life scientists for counsel about assessing the BW threat, on to measures of personal self-protection, and to the political decisions to reallocate resources from other goods to public BW defence. My policy remarks are blatantly US-centric, but can be adapted to any polity dedicated to peaceful order. They have to be datestamped August 2002, as events transpire beyond imagination in this field.

History of BW: War and Disease

Disease has accompanied war throughout history, and before. The second paragraph of the Iliad refers to pestilence:

> And which of the gods was it that set them on to quarrel? It was the son of Jove and Leto; for he was angry with the king and sent a pestilence upon the host to plague the people, because the son of Atreus had dishonoured Chryses his priest.

and divine vengeance is famously recounted in Exodus (9; Plague of Boils):

> And it shall become small dust in all the land of Egypt, and shall be a boil breaking forth with blains upon man, and upon beast, throughout all the land of Egypt.

Recorded history is rife with great plagues. The European conquest of the New World was problematic, but for the ravages of measles and smallpox which proved to be far more brutal than a few muskets and cavalry. The biological expansion of Europe has been described as 'ecological imperialism' by Alfred W. Crosby – with a displacement not only of indigenous people, but also of many native plants and animals. The traffic was two-way, as testified by crops like maize and potato. While most of the biological invasion was probably incidental, there were episodes of the use of smallpox-infected blankets by North American British troops fighting American Indians, and perhaps in internecine Indian warfare as well. So through the nineteenth century, BW was happening, but only sporadically, and prior to the scientific foundations of the germ theory of disease laid down in the 1880s by Louis Pasteur and Robert Koch. There was enough to deal with in public health; BW was not a high priority concern among military planners or the general public.

The turning point in BW-consciousness was prompted by the use of chemical weapons (CW) during the latter years of World War I. Large-scale stocks of chlorine and mustard gas were a byproduct of a chemical industry in which Germany was world leader. The post-World War I mood of pacifist disarmament was also coloured by a determination to weaken any ongoing German advantage. This was manifest in the negotiation of the 1925 'Geneva Protocol', on the face of it a solemn abnegation of all CW, and BW thrown in for good measure. The hortatory language of the protocol is impressive!

> Whereas the use in war of asphyxiating, poisonous or other gases, and of all analogous liquids, materials or devices, has been justly condemned by the general opinion of the civilized world; and … That the High Contracting Parties, … agree to extend this prohibition to the use of bacteriological methods of warfare….

There were three main catches:

1. 'General opinion' notwithstanding, the legal form of the treaty is a contract, binding on its face only on mutual signatory partners.

2. France promptly churned out a reservation, that it would not be bound in the event of a violation by others. Hence the treaty was merely a 'no first use' declaration. Nor were there restraints on the development and stockpiling of BW and CW, short of actual use.

3. The US Senate, in a political mood of isolationist withdrawal, and having torpedoed the League of Nations, withheld US ratification of the treaty, notwithstanding that US diplomats had played a major role in its negotiation.

In effect, then, the Geneva Protocol legitimized further development of biological weapons, despite its promises of no first use. Such development hardly materialized between the wars except for long secret experiments during the Japanese incursion into China before and during World War II.

Japan, Italy and Germany were the only powers actively rearming until the brink of World War II. Italian troops used chemical weapons in Abyssinia. German development of BW was more rumour than fact, but the rumour inspired aggressive rebuilding of CW and BW on the part of the US, strategized by the Merck Committee in 1942. This included the organization of a BW development facility at Fort Detrick, and the mobilization of a substantial cadre of academic microbiological expertise. Mutual deterrence, spurred further by Corporal Adolf Hitler's personal experience as a victim of chemical attack during World War I, appears to have been effective. Substantial stockpiles ready to be deployed were held in abeyance.

One fruit of the bioweapons research was the elevation of anthrax as the agent of choice (and it remains so to this day). However, Aldous Huxley's *Brave New World* (1931) already gives credit to anthrax for the downfall of liberal civilization. Following World War II, BW development was a footnote to the nuclear arms race between the US and USSR. It was much more difficult to keep score, as overhead satellites could do little to reveal stockpiles and development activity. Up to the mid 1960s, Fort Detrick and its British counterpart at Porton Down reflected cutting edge microbiological technology in the West. Lacking contrary evidence the same had to be assumed for the Soviets. A counter-movement began in the US, largely sparked by microbiologists who were uneasy about the takeover of that science for military purposes, and who foresaw the consequences of an unbounded arms race. This gathered momentum along with outcries about the use of herbicides and tear gas in Vietnam, and led to popular pressure for adoption of the Geneva Protocol and stronger BW cum CW disarmament measures. The Nixon administration was not about to concede on the CW side, but in 1969 agreed to (1) a unilateral termination of US BW development and stockpiles, and (2) adhering to British proposals at the UN disarmament conference to progress with a BW Convention (BWC), severing CW disarmament for later, separate consideration. For a time, the Soviets resisted, but at a juncture when US–Chinese rapprochement presaged diplomatic isolation, they eventually concurred, with a convention signed in 1972, and ratified and brought into force in 1975.

The hortatory language of 1975 is no less noble than that of its 1925 predecessor:

> Determined, for the sake of all mankind, to exclude completely the possibility of bacteriological (biological) agents and toxins being used as weapons,...

The record of compliance is somewhat less reassuring: as early as 1979 an outbreak of anthrax in Sverdlovsk (now again Yekaterinburg) was an alarum that the Soviets had continued clandestine BW development. Moscow offered little cooperation to clear up this further provocation in Cold War antics. Nevertheless, BWC-1975, despite its puny machinery for verification and enforcement, did at least set the norm of international behaviour, the delegitimation of this category of weapons. As a practical outcome it drove the technology race underground, and doubtless slowed it up substantially. It confirmed Nixon's 1969 executive order in taking the US out of that race altogether. Continued BW development in Russia may be suspected to this day, but its greatest harm for now is setting a bad example, and leakage to other parties, rather than a plausible threat of actual use by Russia.

The BWC hence provides a legal, ethical, and political base for further steps to investigate and punish transgressions. That base demands reinforcement via public diplomacy towards the establishment of a consensual political will for BW disarmament 'for the sake of all mankind'.

The current status of the BWC is clandestine noncompliance on the part of a dozen nations, at least for underlying development. Iraq is outstanding in having had a major BW development programme revealed mainly through defections of its principals, rather than the sporadic opportunities for international inspection. Aggression among major states can be moderated by deterrence, by the prospects of severe retaliation with other weaponry. For these reasons, our greatest concerns involve smaller states like Iraq, and then of course sub-state threators, the terrorists of every coloration. These may be helped along by provision or pilfering of weapons and expertise from state programmes, or may be entirely indigenous.

The bioterrorist threat is no longer abstract, as shown by the anthrax-by-mail episode of October 2001. A barrage of letters, postmarked Trenton, NJ, containing dry anthrax spores, were addressed to news media and government officials.

Of a dozen confirmed cases, five were lethal inhalational anthrax. These cases were predominantly among mail-handlers rather than target addressees, and included at least two victims likely to have received mail that was contaminated by cross-exposure in a postal facility. At this writing, the FBI investigation proceeds; press speculation about the culprit ranges from a mad South African scientist to Saddam Hussein. As soon as the disease was confirmed, chemoprophylaxis with ciprofloxacin was recommended for those perceived to have been proximately exposed. Some 32 000 people received the antibiotic under supervision of public health authorities. Doubtless as many again were self-medicated. Postal Service and the US Congress were disrupted by the need to institute and verify cleanup. Of many lessons learned, two were

1. Anthrax could be dispersed without sophisticated technology beyond that needed to produce the spore dusts.

2. Modest levels of casualties could disrupt civil life far out of proportion to the objective damage. During the attack, it is difficult or impossible to know exactly who is at risk. Eventually the whole population will be clamouring for care and cure.

The payloads delivered by the letters aggregated perhaps 10 grams. It is easy to imagine scenarios involving 10 kg of spores – at least if the resources of a state threator are engaged, and more efficient aerosol dissemination to boot. So we might be contemplating 100 000 casualties. That toll might be mitigated by many obstacles: uncertainties about potency of strains; technical details of processing; vagaries of weather; preemption by intelligence and law enforcement agencies. But the terrorist attacks of 11 September 2001 erased any optimism about bounds to the motivation to wreak harm. Those intentions, coupled with accessibility of BW capabilities, render a bioattack on this scale as likely as the exchange of nuclear weapons that transfixed us throughout the period of the Cold War.

Amidst all these security concerns, the megathreat of BW commands our attention for preventive and remedial measures at every level:

- pathobiology science
- diagnostic indications and warning
- vaccine prophylaxis and antimicrobial readiness
- public health infrastructure
- environmental assessment and cleanup
- intelligence about threators
- law enforcement
- international diplomacy
- military deterrence and intervention

Indeed every day's headlines betoken deep-seated convulsions in government responsibility for these precautions.

Pathobiology

As stated, the scientific foundations for BW (and BW defence) are the same as for medical responses to natural disease. That knowledge can be called upon for designing remedial interventions to mitigate an attack. Unlike explosives or chemical poisons whose outcome is settled in minutes, for BW consequence management can be effective over a period of days, during which medical care can be all important. For contagious infections, ongoing interventions may extend for years or decades, in stemming the worldwide spread of an epidemic. If you have any doubt, contemplate natural outbreaks like HIV.

In principle, any infectious agent could be recruited for BW purposes. That our species has survived many epidemic onslaughts is testimony to the fact that most natural infections are self-limiting or slow to spread. Many bio-agents are difficult to grow or to transmit, perhaps requiring a specific inset vector. Others are relatively fragile – e.g. most sexually transmitted diseases (STDs) – and have a short life on the shelf or in aerosols. That experience cones down to a handful of those most obviously amenable to BW application. Among bacteria readily grown, on everyone's list are *Bacillus anthracis*, *Francisella tularensis* and *Yersinia pestis* – anthrax, tularaemia and plague, respectively. Anthrax stands out as a threat agent, as it readily forms highly durable spores – these can persist indefinitely in shelf storage, and for many hours in dry air. It can cause dangerous skin lesions, but its most toxic effect is when inhaled. However, it is not contagious in humans. This is an advantage in conventional military operations as it can be effectively targeted against an adversary, without attacking the world. Global pandemics would be the practical effect of attacks with highly contagious agents like smallpox or influenza.

There is rampant speculation about *de novo* genetic engineering of even worse threat agents. In one sense of 'worse', this is unlikely; millions of years of evolution are unlikely to be surpassed. More likely for the foreseeable future are modifications of existing pathogens. These enhancements might circumvent our counter-measures: diagnostics, vaccines, antimicrobials. Or they might confer enhanced viability as aerosols, or propensity to spread.

The second or third round of arms/armour competition is fearful to contemplate. Consequence mitigation is our most urgent current need. In the long run, security must be sought ever more through primary prevention as a commitment of all humane polities – the warning that has been sounded from the start of the nuclear age.

Diagnostic Indications

The latent period between initial exposure to a pathogen and the onset of intractable disease may range from hours to weeks. Hence consequence management, perhaps better said as consequence mitigation, faces challenge and opportunity in the early detection and diagnosis of a bioattack. Establishing just which disease is in question, and in some way modelling the range of exposure are the first priorities. Only then can public health resources be intelligently mobilized for rescuing infected individuals, preventing further spread, and reassuring the public that the outbreak is in process of being contained. Then it becomes important to confirm whether a bio-outbreak was malevolent, and who were the likely culprits, Conventional culture methods – agar plates with indicator media – remain the gold standard for identification of bacterial attack: they are only modestly expensive, and comparably sensitive. New technology, depending on either immunoassays or DNA amplification with polymerase chain reaction (PCR), is on its way to the field. Impressive in the laboratory, many exemplars are just now being extensively tested under realistic field conditions. The cutting edge instruments are expensive, but may be expected to yield to Moore's law of rapidly diminishing costs of electronic technology with time and with volume of production. The dilemma is the infinity of locations to which these 'smoke alarms' should be deployed; their specificity with respect to background interference and intentional hoaxes; and the organizational protocols defining the character of response to the warning. There is also the prospect that future bioattacks will entail agents not in the current roster; methods are being sought that would respond to any pathogen, regardless of its nucleic or antigenic specificity.

Meanwhile there is much attention to early clinical diagnosis. Yes, this means awaiting the first human casualties, but at least wasting no time after that point in recognizing new pathology, and alerting public health of a looming attack. This is what prevailed in October 2001 with anthrax. At the beginning, we could not be certain whether the first few cases were simply the harbinger of a megascale threat. The first cases might be those having idiosyncratic sensitivity to, say, anthrax; or those who were unlucky enough to receive massive doses, accelerating the onset of clinical disease. Environmental monitoring thus remains important for modelling the outbreak even after clinical cases have been reported. The urgency of improving this diagnostic technology, and of systematic analysis of courses of action, is self-evident.

Public Health Infrastructure

Throughout most of the twentieth century, major advances in population health were the fruit of government-based public health – improvements in sanitation, water and food supply, public education (e.g. with respect to STDs), case finding and quarantine, eventually community-wide vaccination programmes. Since the 1950s diagnosis and treatment applied to individual health care has acquired robust scientific foundations. That technology is costly and avidly sought: it has engaged political interest and social budgets which have vastly overtaken the public health interventions, by a ratio today of at least 20:1. Health interventions are assessed today more by the criterion of universal and affordable access to medicine, rather than the measures of health outcomes. In infectious diseases, the US public health infrastructure has deteriorated, with widely varying standards from state to state in disease reporting and childhood vaccinations. Since 1980, remaining resources have been substantially co-opted by one overriding mission, namely AIDS. But that same infrastructure, spanning municipal and state health departments, as well as the national Centers for Disease Control, will inevitably have prime responsibility for the management of disease outbreaks, whether BW or natural. Suddenly with new alerts about BW, the funding picture has been drastically upgraded. It will remain important to maximize the dual utility of that defensive creation, and ensure that the most professional expertise is engaged with it.

Vaccine Prophylaxis and Antimicrobial Readiness

Common childhood viruses like measles might be numbered among the most grievous BW threats were it not for the success of prophylactic vaccines. We could have similar aspirations for BW-oriented viruses, except that (a), As we have learned with AIDS, not every vaccine is so readily developed, and (b) investment in other potential diseases has little incentive from market conditions. Unless the government decides to stockpile a vaccine for future contingencies, who will buy it in the volume needed to recover investment and liability costs?

At this time the number of major pharmaceutical providers of vaccines in the US has shrunk to two.

Government (i.e. taxpayer) dollars are also scarce and valuable resources, and there needs be much further debate about which agents new vaccine development and procurement should be directed at, and to what extent. Besides the production costs, we also have to face many concerns about side effects of a vaccine, especially if it is widely administered in anticipation of an attack that may or may not ever materialize.

Antibiotics generally have fairly broad range of action, and it may be neither necessary nor desirable to invent new ones to deal with BW. However, the massive routine use of antibiotics, not always medically appropriate, has led to natural selection of a host of antibiotic-resistant pathogens, an ever more serious problem in medical management of infectious disease. The counterpart may be the artificial production and use of antibiotic-resistant BW agents. Coping with these will call upon an extended repertoire of remedies. However, as with vaccines, the private sector has become disenchanted with antibiotics as an area of investment for the research, development and certification of new therapeutics.

The US government has decided to procure major stockpiles of important established antibiotics, and of smallpox vaccine to be available in emergency.

Antivirals to treat an infection would be a particular boon, if they allowed the prospect of forgoing their administration until an attack had been confirmed. However, the discovery of molecules, with a favourable therapeutic index, faces formidable challenges because virus metabolism is so closely intertwined with that of the host cell. New genomic and proteomic technologies offer great promise for locating virus-specific targets; but, again, industry has been loath to invest heavily for lack of assurance of markets and prices that would justify the financial risk.

Environmental Assessment and Cleanup

The aftermath of any massive BW attack would be a contaminated site that needs to be contended with after the emergency of victim care. Indoors, machinery – as exemplified by postal processing – complicates the task; outdoors many square miles and vital infrastructure may have to be scrutinized. For tasks like these, our environmental monitoring technology is very primitive. We have difficulty in selecting effective but environmentally safe disinfectants. Above all, we hardly know where to set the limits of a tolerable level of contamination. As with radiation and certain chemicals, our analytical instruments are almost too sensitive. Often we do not know what level of risk is attendant on barely detectable residuals, and policy judgements still have to be made, debated, and accepted as to the tolerable thresholds. It would be helpful in reaching these judgements to know much more than we do about 'natural background' levels of, say, anthrax spores in rural environments.

Intelligence and Law enforcement Concerning Threators

We turn now to roles of government that may severely impact on the conduct of life science, and ideally will also call upon the highest scientific skills. Obviously the best time to stem a terrorist attack is while it is still an intention in the mind of a conspiratorial group. Foreign intelligence operations are beyond the scope of this article. However, the interpretation of fragmentary and ambiguous data will call upon a range of skills that have little history of interface with intelligence organizations. Comparable enhancements are needed when contemporary forensics speaks of genetic deviance in anthrax cultures as a measure of when (and perhaps where) they were cultured.

Government is also concerned, perhaps inordinately, about access to cultures of pathogens that are used in day-to-day experimentation in many laboratories, within the US as well as throughout the world. Regulatory procedures are being posted that would limit access of certain non-US nationals to laboratories working with 'select agents'; others are being emplaced that would require registration of all such laboratories. There is talk of censorship of scientific publication that might facilitate a threator's engineering a new viral BW agent. If there are further BW attacks, even on a modest scale, we can be certain of burgeoning limitations on the freedom of research, for fear of its subversion by the malevolent.

International Diplomacy and Cooperation

Every organized state – so it is not an exaggeration to say civilization – is at risk of severe disruption at the hands of modestly numbered and financed bands of threators who choose to play BW. They may even unleash epidemics of global import. The wisest statesmen have understood how we all face a common threat, and have put their weight behind measures like the BWC. They have even understand how national programmes of BW development will also backfire. Smaller states are equally at risk. But they are also tempted to level the playing field of international power politics, and they will need a nudge from their friends as well as adversaries to adhere to the BWC regime.

This sense of urgency about the BWC does not yet permeate every rank of international polity. It may be up to microbiologists and physicians to communicate what is at stake to their own electorates and leaders, just as eventuated in the US in the late 1960s leading to the BWC.

Perhaps most telling would be renewed commitment on the positive side, for the control of infectious disease globally, in which every nation has a stake, for which the technically advanced can still contribute much by way of resources and of scientific energy. So long as tuberculosis, malaria and AIDS remain so rampant, we can hardly boast of having saturated our capacity to apply medical science for human benefit. Besides the moral gain, there is the cognitive one of nourishing new ideas, of which we have such a dearth, on how to combat BW. All these efforts have to be promoted on an international basis.

Military Intervention and Deterrence

This is a bizarre heading for an encyclopedia of life sciences, but it is the instant implication of biological weaponry. The pursuit of Al Qaida in Afghanistan foretells what may be ultimate decider of the fate of would-be or actual users of BW. Already during the Gulf War in 1991 there was grave concern about blowing up BW facilities for fear of unleashing an epidemic in the region. This is also a metaphor for the likelihood of retaliation with BW on Saddam Hussein's part when the tiger is really cornered.

America has weaponry of unprecedented precision for selective strike. How to target for maximum compellent effect, minimizing unintended casualties, needs further subtlety – fidelity of intelligence being the first requirement. The effects of bombing a BW production or storage site need to be better understood. So, yes, a modicum of microbiology is to be called upon for the most humane reasons in the conduct of war.

From the time of the Neolithic, and on past the Bronze Age, the technologies of working stone, copper and iron have had some impact on agriculture, but mostly on weaponry. The technologies of chemistry and nuclear physics had their turn in the twentieth century. Warfare in the twenty-first century promises to be dominated –

how far indeed can we look ahead – by biology and informatics. Only with extraordinary socio-political foresight can we design reliable ways of domesticating science and technology so that each advance is not promptly coopted for geopolitical advantage. Military investment played a large role in promoting both nuclear physics and computer technology in the middle of the twentieth century. Today the peaceful uses of telecommunications, computers and biotechnology command proportionately much larger investments than the military. Nevertheless, technological development inexorably feeds more weapons. Further, unless special precautions are taken, complex, interwoven technological systems may be even more vulnerable to disruption by evil-doers: for example the safeguards needed to protect nuclear reactors.

Contemplation of sub-state threators yields further headaches: is there any way they can be deterred? For part of the answer, we need an Encyclopedia of Islamist Motivation, which would be a thin book at the hands of today's tiny community of recognized expertise. That's just the start; terrorism has been rife in many other quarters, if so far at a lower scale of violence. Who knows what the example of 11 September will bring forth?

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http://www.vnh.org/MedAspChemBioWar/ for Textbook of Military Medicine

http://www.nlm.nih.gov/medlineplus/ search bioterrorism, anthrax, etc.

www.sipri.se

An outstanding resource on the history of chemical and biological warfare is the series of publications under the headings 'The problem of chemical and biological warfare' and 'SIPRI chemical and biological warfare studies' dating from 1971 to the present. Issued by the Stockholm International Peace Research Institute.

